REMARKS

The Claim Amendments

Claims 1, 8-10, and 26 are pending. Claims 2-7 and 11-25 were previously canceled as drawn to a non-elected invention. Claim 1 has been amended to recite that the expression of UP nucleic acid is determined in the presence of the test agent compared to the expression in the absence of the test agent, wherein a difference between the expression of UP in the presence of the test agent compared to the expression in the absence of said test agent identifies the test agent as a candidate beta catenin pathway modulating agent. Support for the amendment is found throughout the specification.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

Claim Objections

The Office objected to claim 1 because the lines are crowded too closely together. Applicants have corrected the spacing. Accordingly, Applicants respectfully request withdrawal of the claim objection.

35 U.S.C. § 103(a) Rejections

Claims 1 and 8-10 remain rejected under 35 USC § 103(a) as allegedly being unpatentable over WO 03/052068 (Costa) in view of Liu et al, Cancer Research 58:5418-5424 (1998). Applicants respectfully traverse the rejection.

The Office has maintained the rejections for the reasons of record as set forth in the Office Action mailed on September 9, 2008. Briefly, the Office Action alleged that Costa et al. teach a method of identifying a candidate beta-catenin pathway modulating agent comprising providing a PMO antisense oligomer to an assay system and detecting the difference between the test sample and the control (reference) sample in the assay system. The Office stated that Costa et al. do not teach that UP is one of the beta-catenin modifier genes. The Office alleged that Liu et al. teach that human uridine phosphorylase activity is up-regulated in tumor tissues compared to normal tissues and suggest that blocking UP activity may provide strategies for treating tumors. The Office argued that since Costa et al. provided methodologies for identifying a beta-catenin modifier gene and since UP activity was known to be significantly elevated in tumor cells and therefore implicated in cell proliferation as taught by Liu et al., one would have necessarily identified UP as one of the beta-catenin modifier genes and therefore would have used a UP PMO antisense oligonucleotide in an assay system and verified that the UP PMO antisense oligonucleotide is a beta-catenin pathway modulating agent. The Office thus concludes that the claimed invention would have been *prima facie* obviousness.

Contrary to the Office's allegations, the teachings of Costa et al. and Liu et al, alone or in combination, do not render obvious the present invention. The instant claims are directed to a method of identifying a candidate beta-catenin pathway modulating agent comprising the steps of: (a) providing an assay system comprising a UP nucleic acid; (b) contacting the assay system with a candidate test agent; and (c) detecting a change in the expression of UP in the presence of the test agent compared to the expression in the absence of said test agent. Thus, the present claims utilize an assay system comprising a UP nucleic acid to identify a candidate beta-catenin pathway modulating agent.

First, Applicants submit that one skilled in the art would not have been motivated to combine the teachings of Costa et al. and Liu et al. Costa et al. is directed to a screening assay for identifying a beta-catenin pathway modulating agent. Through

specific testing in a *c. elegans* system, the patentees in Costa et al. identified and named several nucleic acids involved in beta-catenin regulation: (1) RAG1AP1, (2) NOP16, (3) LOC87549, (4) DLG4, (5) DLG3, (6) DLG1, and (7) DLG2. Costa et al. did not identify any other genes involved in beta-catenin regulation; nor did they suggest seeking further genes to be used in the assay. In fact, it is apparent from a reading of Costa et al. that all of the genes found to modulate beta-catenin were disclosed in Table I. Given that Costa et al. provides several genes that can be used in the assay to identify a beta-catenin modulating agent, one skilled in the art would not have been motivated to seek the use of alternative genes. Why would one prefer to seek and test yet another new nucleic acid, rather than simply use the nucleic acids that had already been shown to modulate beta-catenin and therefore determined to be useful in the described screening assays? Costa et al. makes no mention whatsoever of the UP gene, much less contemplates or suggests using a UP nucleic acid in the described assay.

Furthermore, Costa et al. makes no mention whatsoever of the UP gene, much less contemplates or suggests using a UP nucleic acid in the described assay. Thus, even if, for the sake of argument, one skilled in the art would have been motivated to seek the use of a new, unidentified, untested nucleic acid rather than use a nucleic acid known to be useful in the described screening assay, given that Costa et al. provides no teaching whatsoever related to the UP gene, one skilled in the art would not have been motivated to specifically seek the use of a UP nucleic acid, including the teachings of Liu et al.

The Office states in the present Office Action that "the *KSR* decision forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness". (Office Action page 3). Contrary to the Office's statement, the Supreme Court in KSR affirmed the utility of the TSM test and merely warned against application of the test in a manner that would result in "[r]igid preventative rules that deny recourse to common sense." Thus, the Court did not foreclose application of the TSM test, it merely emphasized the flexible nature of the TSM test. In fact, the KSR court stated "[o]ften, it will be necessary for a court … to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent

at issue." *KSR Int'l Co. v. Teleflex, Inc.*, 550 US 398, 127 S. Ct. 1727 (2007). And "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does." KSR at 1741.

In fact, the KSR court specifically pointed out that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR* at 1740. Rather, the Court held that "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". *Id.* Thus, the Court left undisturbed the requirement that an examiner must present a "convincing line of reasoning supporting a rejection." MPEP §2144.

The Office argues that one of ordinary skill in the art would have been sufficiently motivated to combine the teachings of Costa et al. and Liu et al. because Costa et al. taught assay methods for identifying a candidate agent that modulates beta-catenin pathway that is implicated in cell proliferation and apoptosis and because Liu et al. taught that UP is up-regulated in tumor cells and thus negatively modulating UP activity by making a UP inhibitor candidate agent may provide cancer therapeutic approaches. Office Action, page 3.

However, the Office still does not provide a rational basis for why one skilled in the art would have chosen a UP nucleic acid out of the hundreds of genes that are "up-regulated in tumor cells" for use in an assay to identify candidate beta-catenin modulating agents. The fact is that, prior to Applicants' disclosure, there was no reported nexus between beta-catenin and UP and no indication whatsoever that UP was involved in the regulation of the beta-catenin pathway. The fact that UP is up-regulated in tumor cells does not amount to a suggestion that it is involved in modulating the beta-catenin pathway. There are numerous genes and pathways involved in the regulation of cell proliferation and oncogenesis. UP could be involved in any of numerous pathways involved in the regulation of cell proliferation. The teaching in Liu et al. in no way

suggest that UP is involved in the regulation of beta-catenin.

The Office further argues that Costa et al. expressly taught that "MBCAT [beta-catenin modifiers] can be identified by detecting 'cell proliferation changes produced by the originally identified candidate agents' by using cells of animals 'predetermined to have a disease or disorder implicating the beta-catenin pathway' such as cancer", referring to page 5, lines 9-16 of the Costa reference. The Office used this teaching to argue that Costa et al. suggested to one of ordinary skill in the art that the potential MBCAT candidate agent can be more expeditiously identified by narrowing the pool of candidate agents to those that produce cell proliferation changes in cancer cells.

However, the Office's contention that Costa et al. expressly taught that "MBCAT [beta-catenin modifiers] can be identified by detecting 'cell proliferation changes produced by the originally identified candidate agents' is misguided. Costa describes various methods. In one embodiment, Costa et al teaches a method of identifying a candidate beta-catenin pathway agent using an assay system that measures or detects changes in (1) RAG1AP1, (2) NOP16, (3) LOC87549, (4) DLG4, (5) DLG3, (6) DLG1, or (7) DLG2 only (i.e., the assay does not require measuring beta-catenin). In another embodiment, Costa et al teaches a method in which the initial identification is optionally confirmed by additionally employing a second assay system (i.e., in addition to the first assay system) that detects changes in the beta-catenin pathway. Thus, the Costa et al reference to which the Office refers (page 5, lines 9-16) actually states that "candidate beta-catenin pathway modulating agents are further tested using a second assay system that detects changes in the beta-catenin pathway, such as angiogenic, apoptotic, and or cell proliferation changes produced by the originally identified candidate agents". Costa et al. teaches an assay in which beta-catenin modulation is optionally measured only as a means of confirming the candidate's ability to modulate beta-catenin once it has been determined that the candidate modulates (1) RAG1AP1, (2) NOP16, (3) LOC87549, (4) DLG4, (5) DLG3, (6) DLG1, or (7) DLG2. Thus, the phenotypic effects observed with beta-catenin modulation (i.e. cell proliferation changes) is NOT used to identify a beta-catenin modulator and, but merely to confirm modulating activity once the modulator has been identified. Costa et al. does not provide any information or guidance as to

which genes modulate beta-catenin other than the seven genes listed in Table I.

The Office further stated that at the time the invention was made, it was known in the art from the teachings of Liu et al. that UP activity is involved in cancer cell proliferation and that an inhibitor of UP, 5-benzylacyclouridine (BAU) had already undergone clinical trials for its ability to inhibit UP and its potential to treat cancer. The Office reasoned that a skilled artisan would have pursued UP over other genes because UP is an art-recognized cancer target gene worthy of clinical research, expenses, and time, and there were not "hundreds of genes implicated in cell proliferation" that were worthy of such involved investment in the art. The Office concluded that given the clinically validated finding that UP activity produces cell proliferation changes in cancer cells and the specific teaching of Costa et al. that a beta-catenin modulator is an agent that produces cell proliferation changes in cancer cells, one of ordinary skill in the art would have had a good and sufficient reason to pursue UP as a potential modulator of beta-catenin pathway that regulates cell proliferation of cancer cells.

However, the Applicants maintain that there are hundreds of genes implicated in cell proliferation in cancer cells, many of which are currently being studied in pre-clinical or clinical trials for the treatment of cancer. Simply because a gene is involved in the regulation of cell proliferation does not suggest that it is involved in the beta-catenin pathway. Likewise, there are also dozens of pathways in addition to the beta-catenin pathway that are involved in cell proliferation and oncogeneis/tumorigenesis. UP could be involved in any of a number of pathways that do not involve beta-catenin. Simply because two genes or a gene and a pathway are involved in the regulation of cell growth does not amount to a suggestion that they are involved in the same pathway or that one modulates the other. Thus, in the absence of any teaching or suggestion to pursue the use of a UP nucleic acid, one skilled in the art would have had no reason to select a UP nucleic acid over the hundreds of other possible nucleic acid molecules and would have had no reason to seek the teachings of Liu et al. It appears that the Office is suggesting that it would have been obvious for one skilled in the art to try targeting UP to identify a beta-catenin modulating agent.

The Federal Circuit has recently clarified the standard for finding obviousness based on an "obvious to try" situation. *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). Reaffirming its prior holdings in *In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988), the Federal Circuit explained that in order for an "obvious to try" situation to serve as the basis for obviousness, some direction in the prior art that would provide a reasonable expectation of success is still required. *Id. See, O'Farrell,* at 903-04. In so doing, the court identified certain circumstances in which a "reasonable expectation of success" is not found and held that the "obvious to try" standard is not appropriate to show obviousness in these circumstances. *In re Kubin*, 561 F.3d at 1360; *In re O'Farrell*, 853 F.2d 894 at 903 (Fed. Cir. 1988). For example, it is improper to hold a claim obvious when:

(1) what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful

or

(2) what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *Kubin*, 561 F.3d at 1359; *O'Farrell*, 853 F.2d at 903.

Likewise, the Court in *In re Lilly and Co.* indicated that the impermissible "obvious to try" situation exists when "a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued". *In re Eli Lilly and Co.*, 902 F.2d 943, 945 (Fed. Cir. 1990).

Application of the "obvious to try" standard is not proper in this case. The claims require identifying a candidate beta-catenin modulating agent by detecting a change in UP in the presence or absence of the candidate modulating agent. However, Costa et al. is silent as to which genes other than those listed in Table I are involved in modulating

the beta-catenin pathway. Costa et al. makes no mention of UP gene and thus fails to teach or suggest a method of identifying a candidate beta-catenin pathway modulating agent using an assay system comprising a UP nucleic acid. Liu et al. provides no teaching or suggestion whatsoever that UP is involved in modulating the beta-catenin pathway. Liu et al. merely describes cloning UP gene and describes some of the characteristics of UP, including teaching that UPase activity is 2-3 fold higher in some tumors compared with normal tissue. Liu et al is not at all concerned with what particular genes are modulated by UP. Thus, like Costa et al., Liu et al. fails to recognize any connection between UP and beta-catenin. This is a case in which what would have been "obvious to try" would have been to try each of numerous possible choices (numerous different nucleic acids) until one possibly arrived at a successful result, where the prior art gave no direction as to which of many possible choices is likely to be successful.

Finally, the Office argues that a pre-existing, already-verified nexus between UP and beta-catenin pathway is not required for one of ordinary skill in the art to arrive at the claimed invention. The Office argues that the claimed methods clearly indicate that one can simply identify a candidate beta-catenin pathway modulating agent by contacting an expression assay system with a UP inhibitor agent and detecting differences between the UP inhibitor agent activity and the reference activity. Thus, there is no step that requires one to know that a UP inhibitor is a candidate beta-candidate pathway modulator prior to performing steps (a)-(c). The Office concludes that because the claims are "testing" whether a UP modulator is a "candidate" MBCAT, all that is required for one of ordinary skill in the art to arrive at the claimed methods is a reasonable degree of predictability that the cancer cell proliferation effects of UP may be related or associated with the cancer cell proliferation signaling activity of the beta-catenin pathway.

However, Applicants submit that prior to Applicants' disclosure there was no indication that the cancer cell proliferation effects of UP may be related or associated with the beta-catenin pathway (over any of the other cell proliferation pathways). There was no suggestion in Costa et al, Liu et al., or other known art to modify the teachings of

Costa et al to select a UP nucleic acid out of the hundreds of other possible genes that could have been selected for use in the claimed assay. Even if it were "obvious to try" using UP (which Applicants submit it would not have been), in the absence of any teaching or suggestion of the connection between UP gene and beta-catenin, the results obtained in the instant application would not have been predictable to one of ordinary skill in the art. Thus, there would have been no reasonable expectation (prior to Applicants' instant disclosure) that UP could have successfully been used in an assay to identify a candidate beta-catenin modulating agent. Applicants submit that the Office has engaged in impermissible hindsight reasoning. The Office is using the benefit of Applicants' own disclosure to conclude that one skilled in the art would have known to test a UP inhibitor as a beta-catenin modulating agent.

Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness because it has failed to provide a motivation or reason that would have prompted one skilled in the art to modify the teachings of Costa et al to select a UP nucleic acid for use in the claimed assay. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection of claims 1 and 8-10.

New 35 U.S.C. § 103(a) Rejection

Claim 26 is rejected under 35 USC § 103(a) as allegedly being unpatentable over WO 03/052068 (Costa) in view of Liu et al, Cancer Research 58:5418-5424 (1998) and Elbashir et al. Applicants respectfully traverse the rejection.

The Office alleges that Costa et al. teach a method of identifying a candidate beta-catenin pathway modulating agent comprising providing an MBCAT oligonucleotide such as an antisense oligonucleotide that modifies beta-catenin to an assay system and detecting the difference between the tested sample and the control (reference) sample in the assay system. The Office alleges that Liu et al. teach that human uridine phosphorylase (UP) activity is up-regulated in tumor tissues compared to normal tissues and suggest that blocking the UP activity may provide strategies for treating tumors. The Office alleges that Elbashir et al. teach that siRNAs are a useful research and assay tool for studying and analyzing gene functions in cell biology or

metabolic pathways because they mediate sequence- specific inhibition of target gene in cultured mammalian cells.

The Office argues that it would have been obvious to one of ordinary skill in the art to utilize the teachings and guidelines of Costa et al. as to how to identify a candidate agent that modulates beta-catenin signaling pathway, which would have led the skilled artisan to make and use an siRNA targeted to UP as the candidate agent. Specifically, the Office argues that one of ordinary skill in the art would have been motivated to test whether the cancer cell proliferative activity of UP is related to the cancer cell proliferation signaling of the beta-catenin pathway because Costa et al. explicitly taught the method of identifying a candidate beta-catenin pathway modulating agent comprising an antisense oligonucleotide against a beta-catenin modifier gene and since UP activity was known to be significantly elevated in tumor cells compared to normal cells as taught by Liu et al. The Office further states that since Costa et al. taught that an MBCAT oligonucleotide such as antisense oligonucleotide is useful as the candidate test agent, since antisense oligonucleotides and siRNAs are functionally equivalent, and since Elbahsir et al. clearly taught that one can make and use a target- specific siRNA in mammalian cell culture systems for assay or research purpose, one of ordinary skill in the art would have reasonably made an siRNA targeted to UP and used it as a candidate test agent in the method of identifying a candidate MBCAT of Costa et al.

Applicants submit that the present claims are not obvious for all of the reasons set forth above. Elbashir et al. does not cure the deficiencies of Costa et al and Liu et al. Elbashir et al is directed to siRNA techniques generally and makes no mention whatsoever of beta-catenin or UP. Thus, Elbashir et al. also fails to provide a motivation or reason that would have prompted one skilled in the art to modify the teachings of Costa et al to select a UP nucleic acid for use in the claimed assay or to test a UP inhibitor in the claimed assay. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection of claim 26.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the Examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

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